NEW DRUGS

Migalastat

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Approved indication: Fabry disease

Galafold (Amicus)
123 mg capsules
Australian Medicines Handbook Appendix A

Fabry disease is one of the lysosomal storage disorders. Many X-linked mutations can cause a deficiency of the enzyme alpha-galactosidase A. This results in an accumulation of its substrates such as globotriaosylceramide (GL–3). A build-up of these substrates, particularly in the vascular endothelium, leads to damage in the heart, kidneys and nervous system. Death occurs mainly because of renal failure and cardiac or cerebrovascular complications. Enzyme replacement therapy, with infusions of agalsidase, has been available for several years.

Although alpha-galactosidase A is mutated, it may still retain some enzyme activity. Migalastat works by binding to the active site of the defective enzyme. This stabilises the enzyme enabling it to enter the lysosome. Once inside the lysosome migalastat dissociates from the enzyme allowing alpha-galactosidase A to catabolise the accumulated substrate.

Migalastat should not be taken within two hours of a meal as food reduces absorption by 40%. Most of the dose is excreted unchanged in the urine with a half-life of 3–5 hours. Renal impairment will increase drug exposure so migalastat is not recommended if the glomerular filtration rate is below 30 mL/min/1.73 m^2.

Migalastat has been compared to placebo in adults with Fabry disease. Only 22% had been treated (more than six months previously) with enzyme replacement therapy. In the double-blind trial 28 patients took oral migalastat every other day and 22 took placebo. They had kidney biopsies at baseline and at six months. After six months 41% of the migalastat group had a reduction of at least 50% in the number of GL-3 inclusions in the interstitial capillaries of the kidney. This response was seen in 28% of the placebo group. The median reduction in GL-3 from baseline was 40.8% with migalastat and 5.6% with placebo.[1]

Statistical analysis showed that, overall, migalastat was no different from placebo. The drug was more effective in some mutations than others, so if the results are analysed according to the mutation there is an advantage for migalastat. Post hoc analysis of 45 patients with suitable mutations taking migalastat showed a significant reduction in GL-3 inclusions in renal interstitial capillaries at six months. However, there were no significant differences in glomerular filtration rates at six months. Open-label follow-up at 24 months showed the mean estimated glomerular filtration rate had reduced by 0.3 mL/min/1.73 m^2 with migalastat and by 1.51 mL/min/1.73 m^2 with placebo.[1]

Similarly, treatment with migalastat had no significant overall effects on left ventricular mass in the first six months of the trial. However, when the patients with suitable mutations were analysed there was a significant decrease in left ventricular mass at 24 months.[1]

Another trial compared migalastat to enzyme replacement therapy with agalsidase in adults with suitable mutations. They had been receiving therapy for at least a year. In this open-label trial 36 patients were randomised to oral migalastat every other day and 24 to continue infusions of agalsidase every other week. After 18 months the decline in glomerular filtration rate was similar in both groups. For example, using the estimated glomerular filtration rate method, the annual decline was 0.4 mL/min/1.73 m^2 with migalastat and 1.03 mL/min/1.73 m^2 with agalsidase (>50% overlap of the 95% confidence interval). On echocardiography, there was a significant reduction in left ventricular mass with migalastat. In a composite clinical outcome of renal, cardiac or cerebrovascular events there was an event in 29% of the migalastat group and 44% of the agalsidase group.[2]

Fabry disease can cause debilitating gastrointestinal symptoms. Compared to placebo migalastat decreased diarrhoea and reflux.[1] Other adverse reactions include headache, dizziness, paraesthesia, muscle spasms, rash and weight gain. As for other patients with Fabry disease, there should be regular monitoring of renal and cardiac function.

Fabry disease is rare so the trials only had small numbers of patients. It would therefore be difficult to show a significant difference in effectiveness between migalastat and enzyme replacement therapy. The difference in events was not statistically significant.[2] An oral treatment is likely to be preferred by patients, but only those with suitable mutations seem to benefit. There are over 800 different mutations of which 268 are suitable for treatment with migalastat. At present the benefits of migalastat are based largely on surrogate markers. It remains to be seen whether, for example, by slowing the decline in glomerular filtration rate long-term treatment will lead to less renal failure.

TT manufacturer provided additional useful information

REFERENCES

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2. Hughes DA, Nicholls K, Shankar SP, Sunder-Plassmann G, Koeller D, Nedd K, et al. Oral pharmacological chaperone migalastat compared with enzyme replacement therapy in Fabry disease: 18-month results from the randomised phase III ATTRACT study. J Med Genet 2017;54:288-96. http://dx.doi.org/10.1136/jmedgenet-2016-104178

The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA, the European Medicines Agency and the Therapeutic Goods Administration.